United States Patent [19]

MacGregor

[11] **4,101,984**

[45] **Jul. 25, 1978**

[54] **CARDIOVASCULAR PROSTHETIC DEVICES AND IMPLANTS WITH POROUS SYSTEMS**

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[21] Appl. No.: **683,382**

[22] Filed: **May 5, 1976**

[30] **Foreign Application Priority Data**

May 9, 1975 [CA] Canada 226993
Dec. 22, 1975 [GB] United Kingdom 52474/75

[51] **Int. Cl.**[2] **A61F 1/22; A61F 1/24**

[52] **U.S. Cl.** ..... **3/1.5**; 3/1; 3/1.4; 3/1.7; 128/1 D; 128/92 C; 128/419 P; 427/2

[58] **Field of Search** ..... 3/1.5, 1.7, 1.4, 1, 3/1.9; 128/92 C

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,689,942	9/1972	Rapp	3/1.5
3,855,638	12/1974	Pilliar	3/1
3,914,802	10/1975	Reick	3/1.4
4,017,911	4/1977	Kafesjian et al.	3/1.5

OTHER PUBLICATIONS

"An Experimental Study of the Use of Polyvinyl Sponge for Aortic Grafts" by N.E. Shumway et al., Surgery, Gynecology & Obstetrics, Jun. 1955, pp. 703–706.

"Porous Segmented Polyurethanes–Possible Candidates as Biomaterials" by Garth L. Wilkes et al., Journal of Biomedical Materials Research, vol. 7, No. 6, Nov. 1973, pp. 541–554.

"Aortic Valve Prosthesis," The Bulletin of the Dow Corning Center for Aid to Medical Research, vol. 1, No. 1, Oct. 1959.

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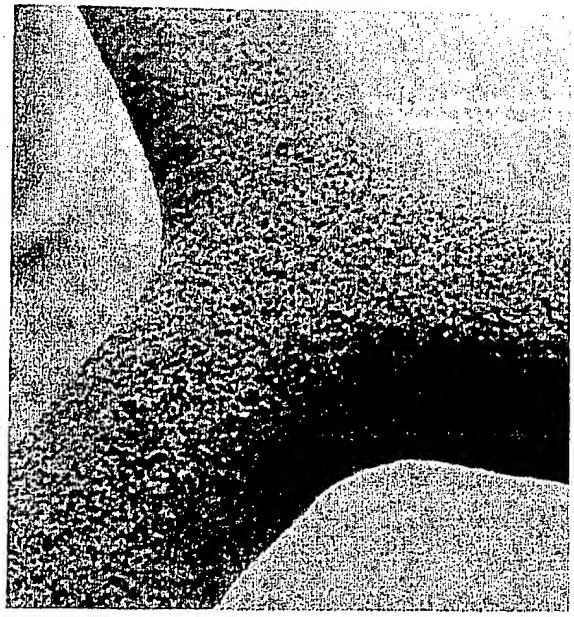
[57] **ABSTRACT**

A novel cardiovascular prosthetic device or implant having many useful cardiovascular applications comprises a porous surface and a network of interconnected interstitial pores below the surface in fluid flow communication with the surface pores. Tissue forms a smooth thin adherent coating of self-determining thickness on the porous surface making it resistant to the formation of the blood clots normally associated with the presence of foreign bodies in the blood stream.

6 Claims, 10 Drawing Figures



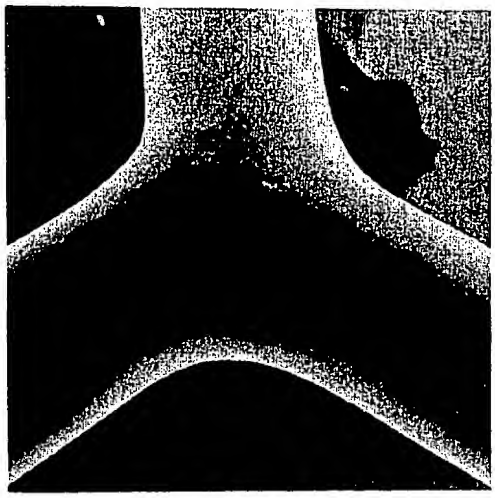


FIG. 1

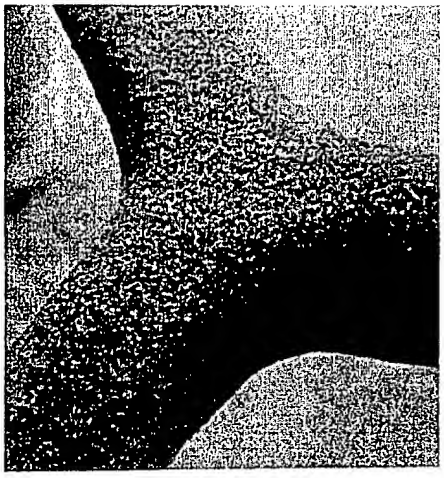
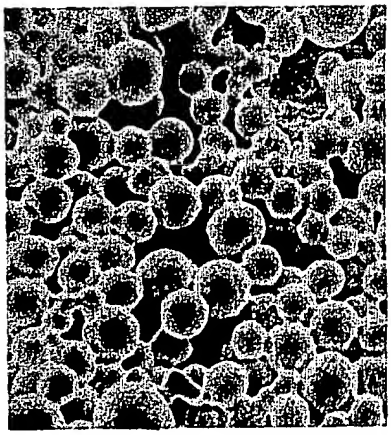


FIG. 2

FIG. 3



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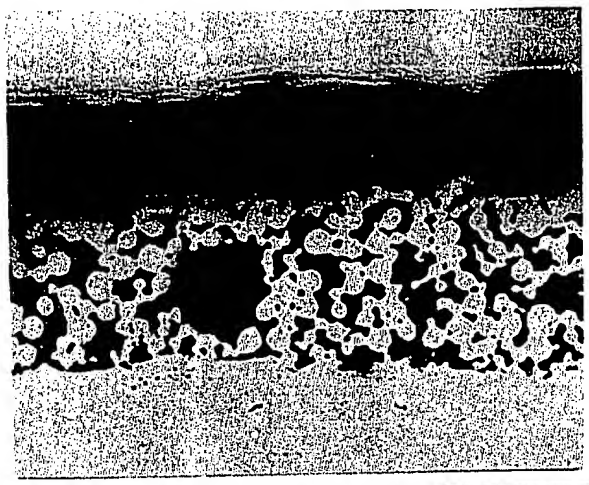


FIG. 5

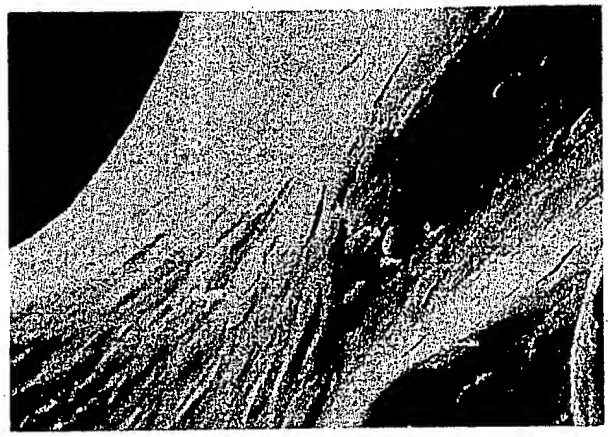


FIG. 6

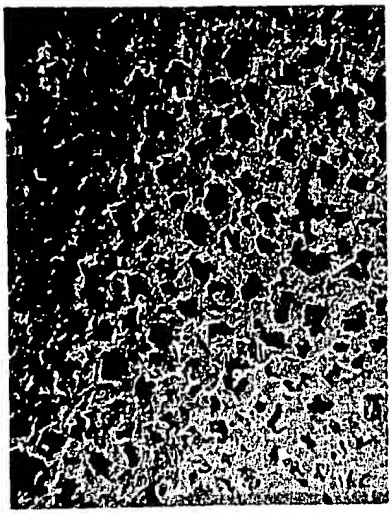


FIG. 7

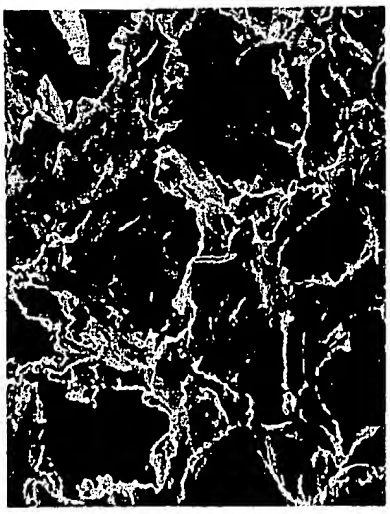


FIG. 8

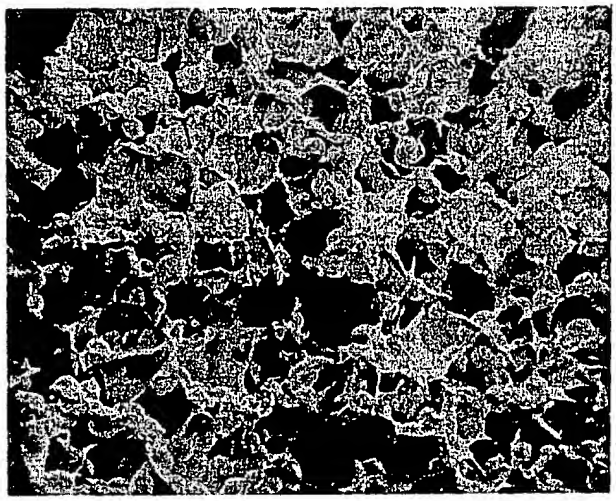


FIG. 9

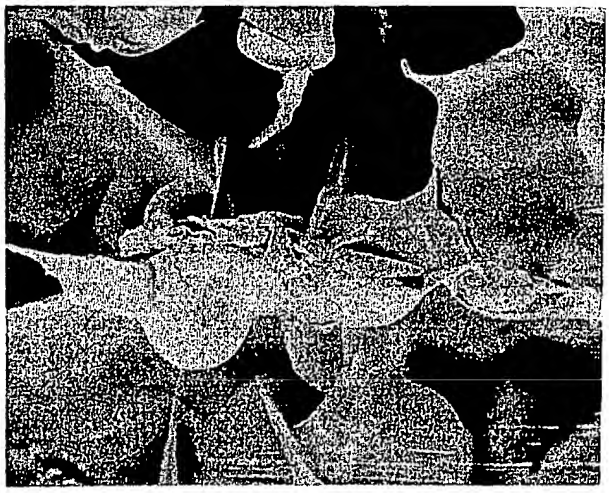


FIG. 10

CARDIOVASCULAR PROSTHETIC DEVICES AND IMPLANTS WITH POROUS SYSTEMS

FIELD OF INVENTION

This invention relates to novel prosthetic devices and implants for cardiovascular use.

BACKGROUND OF THE INVENTION

It is well known that the introduction of foreign bodies into the blood stream, for example, the polished metal surfaces of artificial heart valves, tends to cause the formation of blood clots which may break loose and embolize to various parts of the body. Such thromboembolic problems have led to the administration of anticoagulants to patients with artificial heart valves. The effects of these anticoagulants on the blood clotting mechanism cause difficulties in stopping the flow of blood through even a minor flesh wound. In addition, flexible plastic conduits are used for vascular graft purposes and such surfaces also are thrombogenic.

Attempts have been made to overcome the thromboembolic problems of polished metal heart valves by providing a porous fabric covering over blood-engaging metal parts. When such porous fabrics have been used for covering metal heart valve parts, pores of typical size 500 to 700 microns have been provided and some tissue ingrowth has been observed. While the fabric covering has resulted in a decreased incidence of thromboembolism, apparently due to the observed tissue ingrowth, such valves do suffer from other defects, notably wear of the fabric, causing cloth fragment embolism and chronic hemolytic anemia as a result of turbulence of the blood over disrupted fabric coverings.

To date, the prior art has been unable to provide a heart valve which not only overcomes the thromboembolic problems of a smooth metal surface but also does not exhibit the wear failure problem of the prior art fabric covered heart valves.

SUMMARY OF THE INVENTION

The present invention provides a heart valve which overcomes the prior art defects by providing the blood-engaging metallic parts in the form of a solid substrate having an adherent porous metallic surface coating which has a network of interconnected pores therein. It has been found that the rigid nature of the metal coating, the strength of the substrate-coating interface and the strength of the particle-particle bond in the coating provide excellent strength and wear resistance characteristics while nucleated cells circulating in the blood stream colonize onto the blood-engaging surface of the porous coating and subsequently differentiate into other cell types to form a thin, smooth, generally uniformly-thick, firmly attached tissue covering on the surface. The tissue covering is formed rapidly over about a one month period, does not appear to increase significantly in thickness thereafter, and includes flattened endothelial-like cells at the surface thereof. The tissue formation is not accompanied by thrombosis or embolish owing to its blood-compatible nature, and once the maximum thickness has been attained, the tissue covering is self-regenerating.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 is a photograph of uncoated metal strut members of a heart valve cage at 25 times magnification;

FIG. 2 is a photograph of the strut members in FIG. 1 coated with −500 mesh metallic powder at 25 times magnification;

FIG. 3 is a close-up photograph of the surface of the coating of FIG. 2 at 750 times magnification;

FIG. 4 is a close-up photograph of the surface of the coating of FIG. 2 at 3500 times magnification;

FIG. 5 is a thin section taken through a porous coated metal heart valve element after positioning in the blood stream of a dog for 2 months at 300 times magnification showing the formation and ingrowth of smooth-surfaced endothelialized tissue on the porous surface;

FIG. 6 is an electron micrograph of the tissue surface of composite porous coated metal body after positioning in the blood stream of a dog for 3 months at 700 times magnification showing endothelial cells in the tissue;

FIG. 7 is a photograph of a porous hydrophilic polyurethane element at 20 times magnification;

FIG. 8 is a photograph of the porous surface of FIG. 7 at 100 times magnification;

FIG. 9 is a photograph of a porous polymethylmethacrylate surface at 17 times magnification; and

FIG. 10 is a photograph of the porous surface of FIG. 9 at 90 times magnification.

GENERAL DESCRIPTION OF INVENTION

In U.S. Pat. No. 3,855,638, there is described a surgical prosthetic device consisting of a metal substrate with a porous metal coating into which bone tissue may grow for incorporation of the prosthesis into the body. The porous coating used in this prior art device has several essential requirements, including restrictions on coating thickness, interstitial pore size and coating porosity. These parameters are dictated by the strength requirements of the surgical prosthetic device, namely, that the coating and the coating-substrate interface have strengths at least that of bone, so that there is no danger of failure of the prosthesis after ingrowth of bone tissue.

In cardiovascular uses, however, strength is a less important consideration, and the ranges of parameters chosen are dictated to some degree by the intended use of the prosthetic device or implant.

Further, the mechanism of incorporation of the surgical prosthetic device of this prior art into the body is by ingrowth of tissue into the coating while the present invention involves quite a different mechanism which arises from the different environment of the devices of the invention as compared with that of the prior art.

Heart valves include a plurality of components including an occluder, typically a ball or disc, an occluder seating ring, occluder guide struts, muscle guards to prevent interference by muscle with movement of the occluder and a sewing ring to attach the valve to the heart. The occluder seating ring, occluder guide struts and muscle guards usually are constructed of metal. The occluder may be metal or other material.

In accordance with this invention, the engaging elements of a heart valve are formed as composites having a dense coherent metallic substrate and a rigid metallic porous coating which is adhered to the substrate and consists of metallic particles joined to adjacent particles to form an interconnected network of pores which is substantially uniformly distributed throughout the coating. It may be desirable to omit such coating from substrate surfaces where there is relative movement between members. It is preferred to form the coating from fine metallic particles, typically of −500 mesh size, in

order to minimize abrasion between heart valve elements and hemolysis of the blood. It has been found that porous coatings formed from finer particles provide smoother tissue coatings than porous coatings formed from coarser particles.

It is also preferred to provide a thin porous coating on the metal substrate surfaces in order to provide the maximum orifice for blood flow, and typically the thickness is about 20 to 300 microns, preferably about 50 to about 150 microns.

The shear strength of the composite surface is important, especially where heart valve surfaces are in relative motion, and it is necessary that the composite have a high fatique tolerance, the endurance limit (10^7 cycles) being greater than 500 psi. It is preferred for the surface coating interface and the coating itself to have shear strengths greater than about 1000 psi, more particularly greater than about 3000 psi.

The porosity of the coating portion of the composite varies between about 10 and about 50%.

The invention is not restricted to heart valves but is applicable to a wide variety of cardiovascular prosthetic devices or implants having blood engaging surfaces. In accordance with the invention, the blood engaging surface is porous in nature and has an interconnected network of pores in the subsurface thereof.

The cardiovascular phosthetic devices or implants used in the present invention may be, in some cases, as in the heart valve case as mentioned above, in the form of a porous coating on a coherent substrate, with the network of interconnected pores extending throughout the coating only. Alternatively, the prosthetic device or implant may be wholly porous with the network of interconnected pores extending throughout the body of the device.

An example of the use of the latter type of device is as the metal electrode tip of a heart pacemaker, although the electrode tip also may be provided in the composite form, if desired.

The pacemaker electrode tip and the heart valves use metal as the material of construction. The term "metal" as used herein is intended to include metal alloys. The metal utilized is one which is non toxic to the blood and body tissue. One such material is the cobalt alloy that is known by the trade mark "VITALLIUM".

Where such metal prosthetic devices and implants are of the composite type, they may be formed by a number of techniques involving sintering, the particular sintering procedure depending to some extent on the size of the particles from which the porous coating is formed.

The metal particles from which the porous coating is formed generally fall into one of four categories, namely −500 mesh (less than about 20μ, −325 + 500 mesh (about 20 to about 50μ, −100 + 325 mesh (about 50 to about 200μ and +100 mesh (greater than about +200μ. The term "mesh" used herein refers to the U.S. Standard Sieve mesh size.

In each case, the smooth coherent substrate is first roughened, for example, by blasting with abrasive material.

The coating of metal particles then is formed on the roughened surface. The metal in the substrate and coating usually are the same, but different metals may be used.

In one procedure, a binder for the metal particles first is sprayed onto the roughened metal surface and the device then is suspended in a fluidized bed of powder metal particles to form a coating on the roughened surface. The coated body is withdrawn from the fluidized bed and the binder allowed to dry. This procedure has been found to be satisfactory for each of the particle sizes, except for the −500 mesh particles.

In an alternative procedure, the powder metal particles are mixed with a binder to form a fairly viscous slurry which is spray applied to the roughened surface to form the coating thereon, the coating thereafter being dried. It has been found that this procedure is satisfactory for −325 mesh size particles and below.

In a further procedure, the metal particles and binder are slurried and the roughened surface is dipped into the slurry. Excess material is allowed to run off and the coated body is dried.

In each case, the preform of dried coating and substrate is sintered to cause metal fusion interconnection of the metal particles one with another and with the roughened substrate surface to provide a rigid porous structure having a network of interconnected pores substantially uniformly distributed throughout the coating.

It is possible to build up any desired thickness of porous coating on the coherent substrate by presintering the dried coating to provide some strength thereto and then repeat the coating and presintering operation for as many cycles as is required to build up the desired thickness. When the desired thickness has been achieved, the composite is sintered to provide the required particle-particle and particle-substrate adhesions.

The presintering and sintering temperatures which are preferably utilized depend on the particle size of the metal particles, lower temperatures generally being used for smaller particle sizes.

Thus, for −500 mesh metal particles, presintering preferably is carried out by heating at a temperature of about 2000° F (about 1100° C) momentarily or up to about 10 minutes and then cooling while sintering preferably is carried out by heating at a temperature of about 2150° F (about 1175° C) for about 60 to about 90 minutes in a hydrogen or other reducing gas atmosphere, or under vacuum.

For the −325 +500 mesh metal particles, presintering preferably is carried out by heating at a temperature of about 2100° F (about 1150° C) for about 8 minutes, while sintering preferably is carried out by heating at a temperature of about 2200° F (about 1200° C) for about 60 to about 90 minutes in a hydrogen or other reducing gas atmosphere, or under vacuum.

When metal particles of particle size +325 mesh are used, the presintering preferably is carried out at a temperature of about 2200° F (about 1200° C) and sintering preferably is carried out at a temperature of about 2200° to about 2300° F (about 1200° C to about 1250° C) for about 2 to about 3 hours, in a hydrogen or other reducing gas atmosphere, or under vacuum.

Following formation of the porous coating, it may be machined and refined, if desired, to improve its surface characteristics.

The metal particles generally are substantially spherical, although other geometrical shapes and mixtures of shapes may be used. FIGS. 1 to 4 illustrate part of a typical device provided in accordance with this invention wherein the coating is formed from −500 mesh metal particles.

Thus, the normal polished metal surface struts (FIG. 1) of a heart valve cage, the apex of which is seen in FIGS. 1 and 2, is coated with an adhered rigid porous coating of substantially spherical metal particles, giving

the struts the appearance seen in FIG. 2. In the highly magnified photographs of FIGS. 3 and 4, it can be seen that the metal particles are adhered one to another by diffusion bonded regions to define a plurality of surface pores. The surface pores communicate with a subsurface interconnected network of interstitial pores, as may be seen from the thin section of FIG. 5.

Wholly porous metallic devices may be formed by sintering the metal particles in a mold at the sinter temperatures specified above for the porous coatings. Binders may be used, if necessary.

The present invention is not limited to metal as the material of construction of the prosthetic device or implant and many other constructional materials inert to blood may by used, either alone or in combinations of two or more such materials, provided that they can be provided in a porous form. Typical materials include flexible or rigid plastics, ceramics and carbon.

When plastic materials are used in this invention, they may be provided in rigid form or in flexible form and in wholly porous or composite form. The rigid plastics may be used in similar applications to the rigid metal bodies, as outlined below. The flexible plastic materials, however, have particular utilities not enjoyed by the metal bodies owing to the rigid nature of the metal bodies.

One method of forming a porous polymer structure involves pulverizing the polymer to the required particle size and then compressing the polymer powder at pressures below about 100 psi and at a temperature in the range of about 20° to about 100° F (about 7° to about 38° C).

Another method of formation of porous structures for use in the present invention is to blend together a moldable flexible polymeric material and solvent-elutable particles in quantities to provide a continuous phase of polymer and a dispersed phase of solvent-elutable particles in the blend. The blend may be subjected to compression molding to the desired shape, if desired. The resultant body then is contacted with solvent to remove the solvent-elutable particles to leave an open network of interconnected pores throughout the body.

The solvent-elutable particles and the elution solvent should be non-toxic in nature so that any residual material is not harmful to body tissues or blood in use. Typically, the solvent elutable particles are water-soluble, for example, sodium chloride or sodium carbonate particles.

The particle size of the particles to a large degree dictates the pore size in the polymer body, although irregular shapes generally result.

The pore size, volume and shape in the product may be controlled by varying the size, shape and distribution of the solvent-elutable particles and the weight ratio of the polymer to particles.

As may be seen in FIGS. 7 and 8, a flexible porous hydrophilic polyurethane product formed by the above procedure and using −200 +500 mesh sodium chloride particles, has an open porous structure in which the continuous polymer phase is irregularly shaped.

If desired, the totally porous product may be laminated in a mold or by solvent techniques with a solid coherent flexible polymer body.

Porous flexible polymeric materials have particular utility in the suture or sewing rings of heart valves. Suture rings often are formed of fabric filled with closed cell polymeric foam material. The porous flexible polymeric material having interconnected pores may be used as the polymeric filler of the suture ring.

Alternatively, the flexible porous polymeric material having interconnected pores may be provided as the outer surface of a conventional foam-filled fabric suture ring, either by direct attachment thereto or by attachment through an intermediate solid substrate.

A composite of a porous polymeric material and a solid coherent substrate may be utilized as the suture ring by direct secure attachment to the occluder seating ring. The attachment may be achieved by causing the solid substrate to flow into a porous metal surface of the character described in detail above on the seating ring and harden in the subsurface pores to interlock with the network of interconnected pores, for example, by pressure molding.

The latter procedure may be used, if desired, to provide flexible or rigid solid and/or porous plastic external coatings on rigid metal coatings on other heart valve components, by pressure molding a polymer to the metal coating.

In an alternate procedure for the formation of the flexible porous products, there may be first formed beads of polymer having a core of solvent-elutable material by solution coating of the core material. The beads then are compression molded to the desired shape and the product is leached to remove the solvent-elutable material to leave the porous material. The beads may be pressure molded to a solid polymer body, if desired, to provide a laminated structure after completion of the elution. Alternatively, the wholly porous product from the elution may be attached to a solid polymer body.

A further method of formation of the porous polymeric material is to form a casting solution of the polymer and solvent-elutable particles, cast the solution onto a casting surface, which may be a solid polymer substrate, if a composite structure is desired, and elute the solvent-elutable particles from the cast material.

Polymer coated solvent-elutable particles may be extruded to form tubes or the like when the device is to take this form. Following extrusion, or possibly molding, the tube is leached to remove the elutable particles. The tube may be provided in wholly porous form or may be formed as a laminate having a coherent solid polymeric substrate which has adhered inner and/or outer porous coatings. The laminate structures may be formed by lamination of the polymer coated solvent-elutable particle layers to the core layer prior to leaching. Alternatively, lamination may be carried out after leaching of the solvent-elutable particles from the polymer.

Tubular flexible polymeric materials which are wholly porous or have inner and/or outer porous surfaces adhered to coherent substrate are particularly useful as vascular grafts, particularly small diameter grafts of diameter less than about 6 mm.

Another procedure for the formation of a porous polymeric material is to cast the polymer around a lattice work which may then be rolled or formed into the desired shape.

A further procedure for formation of a porous polymeric material involves providing a powdered solid polymer phase and a solvent phase including a solvent for the polymer. The liquid monomer phase is drawn rapidly through the powder particles so as to allow dissolving of polymer at the surface of the polymer particles only and to cause the formation of particle-to-

particle joints. A typical rigid polymeric porous product formed in this way from polymethylmethacrylate particles of size −100 +325 mesh is shown in in FIGS. 9 and 10. The interconnection of the polymer particles and the porous nature of the product are clearly illustrated therein.

The wholly porous product formed in this latter procedure may be combined with a rigid polymeric member to form a composite structure, if desired.

The present invention may be used for a variety of cardiovascular applications in addition to those specifically mentioned above, including partially or totally implantable blood pumps, such as artificial hearts and ventricular assist devices, heart valve components, such as flexible flap-type valve members, other heart pacemaker electrode parts, rigid or flexible blood vessel grafts and patches, particularly small diameter grafts of diameter less than about 6 mm, blood stream filters, intracardiac patches, diaphragms or baffles and in vascular access tubes.

In the latter case, typically for use in haemodialysis, the inner surface of the tube is porous coated to promote colonization and tissue growth, while the outer surface also may be porous coated for soft tissue ingrowth.

In many applications of the present invention, the promotion of colonization and tissue growth is accompanied by true soft tissue ingrowth into the porous surface at the margins or on the outer surface from adjacent body tissue, to provide bonding between the host and the member, as described in my copending U.K. application Ser. No. 52474/75 filed Dec. 22, 1975.

The body tissue ingrowth combined with promotion of tissue growth on the porous surface from the nucleated blood stream cells is important in many applications of the present invention.

For example, in an artificial heart, a porous coating on all the elements provides a means of fixation to host tissues by soft tissue ingrowth and provides surfaces which are blood compatible arising from colonization and tissue formation on the blood-contacting surfaces.

The formation of the adherent tissue coating from nucleated blood cells also allows the cardiovascular prosthetic device or implant of the present invention to be incorporated into the cardiovascular system, thereby achieving a more secure attachment than has previously been the case.

The porous system interfacing blood in accordance with this invention in order to result in a tissue coating on the porous system also has other uses. Thus, non-cellular material may be sampled through the porous system, for detection of the presence and/or concentration of the constituents.

The interface between the circulating blood stream and an artifical endocrine organ may be porous. For example, an artifical pancreas may be provided in which glucose is sampled through a porous system interfacing with flowing blood and insulin and/or glucagon is released through the porous system and the tissue coating thereon interfacing with flowing blood. The source of the hormones and/or the control circuitry and/or the energy sources may be provided external to the body or may be implanted.

A slow release device interfacing blood may be provided, the device providing slow, sustained release of a substance into the blood through the porous system and its associated tissue coating interfacing the blood. The substance may be a drug, for example for long term antibiotic therapy, or hormones, for example, estrogens and/or progestigens providing a chronic implanted birth control device.

The parameters of the porous surface for use in the cardiovascular prosthetic devices and implants of this invention may vary widely and those chosen depend somewhat on the particular end use of the prosthetic device or implant. The surface must, however, have an interconnected network of pores underneath the surface in fluid flow communication with the surface pores to promote the colonization by nucleated cells and subsequent differentiation into other cell types so that the tissue which is formed and grows in the surface is interlocked in the subsurface network.

The interstitial surface pore size may vary widely, typically from about 1 micron up to about 1000 microns, although it may be preferred to use pore sizes below about 20 microns. As the pore size decreases, the surface becomes smoother, decreasing blood turbulence and abrasion on moving parts of the device.

The porosity also may vary widely, from about 8% upwards, although the porosity is usually in the range of about 10 to about 50%. Where a coating is provided on a coherent substrate, the thickness may vary from a single layer of particles upwards, for example, from about 1 to about 10,000 microns. Thin layers are preferred in devices having close tolerances.

EXAMPLES

The invention is illustrated by the following Examples:

EXAMPLE 1

Twenty-six prosthetic aortic ball valve cages were obtained and the poppets and sewing rings were removed. The metallic surfaces of fourteen of the cages were roughened, ultrasonically cleaned and coated with cobalt-base alloy powders (Vitallium) of various particle sizes to a depth of from about 100 to about 300 microns using the temperatures and times outlined in the following Table I:

TABLE I

Powder Size Mesh	Powder Size (μ)	No. of cages	Temperature	Time
−500	less than 20	2	2200° F (1200° C)	1 hr
−325 +500	20 to 50	6	2330° F (1220° C)	2½ hrs
−100 +325	50 to 200	6	2330° F (1220° C)	2½ hrs

The cages were implanted in the right atria of thirteen dogs, six of the dogs having implanted +500 mesh coated cages, one of the dogs having implanted the −500 mesh coated cages and the remaining six dogs having implanted uncoated cages as controls. The seating ring of each valve cage was fastened to the orifice of either the superior vena cava (SVC) or inferior vena cava (IVC) by an encircling umbilical tape such that the valve struts and their trifurcation were freely suspended in the right atrial cavity. No anticoagulants were given to any of the dogs.

One experimental dog and one control dog were sacrified at 2 weeks, 1 month, 6 weeks, 2 months, 3 months and 6 months after implanation. Upon removal, each valve cage was examined grossly for evidence of tissue growth as well as thrombus formation. The thrombus formation was graded on a scale of 0 to ++++, 0 representing a total absence of thrombus

and ++++ representing total occlusion of the valve cage orifice by thrombus.

Additionally, the lungs were examined grossly for evidence of pulmonary embolism and representative sections of each lobe were taken for light microscopy.

At each time interval, one valve cage was examined by scanning electron microscopy and a special thin section of the other valve cage was prepared for transmitted and incident light microscopy using a low-speed diamond cut-off wheel. After the sections had been prepared, the tissue component was stained with a dilute solution of methylene blue.

The experimental dog containing the 2 valve cages with the −500 mesh powder-made metal surface was sacrified at 2 months . The tissue covering was torn of a portion of one of the valve struts and this area, as well as an area where the tissue covering remained intact, were examined by scanning electron microscopy. A special thin section was prepared from the second valve cage as described above, and is shown in FIG. 5.

All the porous-coated valve cages were found to have developed a thin, semi-transparent, smooth, firmly attached tissue covering with absolutely no evidence of thrombosis or embolism to the lungs. In most instances, the seating ring and base of the struts were totally incorporated into the walls of either the SVC or IVC at their points of attachment. In contrast, no tissue growth occurred on the uncoated valve struts and varying degrees of thrombus formation were observed in 10 of the 12 control valve cages. Additionally there was gross and microscopic evidence of pulmonary embolism in the control dogs sacrified at 2 weeks, 6 weeks, and 3 months.

The results are reproduced in the following Table II:

TABLE II

	Dog Number	Site	Particle Size (Microns)	Implant Time (months)	Thrombus Formation
Experimental	1	SVC	50 to 200	0.5	0
		IVC	20 to 50	0.5	0
	2	SVC	20 to 50	1.0	0
		IVC	50 to 200	1.0	0
	3	SVC	50 to 200	1.5	0
		IVC	20 to 50	1.5	0
	4	SVC	20 to 50	2.0	0
		IVC	50 to 200	2.0	0
	5	SVC	50 to 200	3.0	0
		IVC	20 to 50	3.0	0
	6	SVC	20 to 50	6.0	0
		IVC	50 to 200	6.0	0
Control	7	SVC	uncoated	0.5	+++
		IVC	uncoated	0.5	++++
	8	SVC	uncoated	1.0	0
		IVC	uncoated	1.0	+
	9	SVC	uncoated	1.5	++
		IVC	uncoated	1.5	+
	10	SVC	uncoated	2.0	+
		IVC	uncoated	2.0	0
	11	SVC	uncoated	3.0	+
		IVC	uncoated	3.0	++
	12	SVC	uncoated	6.0	++
		IVC	uncoated	6.0	++

Scanning electron microscopy of the porous surfaces of the experimental valve cages showed a complete tissue covering as early as 2 weeks with the appearance of surface squamous endothelial cells at 3 months as illustrated in FIG. 6. The undulations in the tissue covering produced by the underlying spherical metal particles in both the coarse and medium powder-made surfaces were virtually eliminated by using the fine powder-made surface (particle size −500 mesh), as can be seen from FIG. 5.

Examination of the region in which the tissue covering was torn off the fine powder-made metal surface showed that the tissue had sheared off at the surface of the porous coating leaving fragments of tissue still affixed to the underlying pore structure.

Transmission light microscopy of the thin sections of the porous-coated struts showed the following evolution of the tissue covering. At 2 weeks the porous coating was covered with a material which resembles a platelet-fibrin mesh. Within this mesh were large mononuclear cells which have the ability to differentiate into other cell types. By 6 weeks, fibroblast-like cells had appeared and the porous coating was infiltrated and covered with connective tissue which was loosely textured within the porous coating and more compact towards the surface. Sections examined at 2 months showed well organized connective tissue within and over the surface of the porous coating. Pigment-filled macrophages had appeared and on the outer surface there were flattened endothelial-like cells. By 3 months, there was a uniform layer of connective tissue covering the entire surface of the porous metal coating which was quite compact even in its deeper layers. Again the surface was seen to be covered by flattened endothelial-like cells. Although some blood vessels were observed near the base of the struts where they had been in contact with the caval walls, no blood vessels were present in the tissue covering the struts which were freely suspended within the right atrial cavity. It would appear that the tissue growing on the valve struts was nourished by diffusion from the bloodstream and, as such, can survive without a blood vessel supply from the host.

Finally, the thickness of the tissue over and above the porous coating reached a maximum thickness of about 100μ which was independent of the underlying coating particle size.

EXAMPLE 2

A heart valve cage was coated with −325 +500 mesh Vitallium powder as described in Example 1 and was positioned in the descending thoracic aorta of a dog. After 6 months, the dog was still alive and well, indicating absence of major thromboembolism.

From a comparison of the results of Examples 1 and 2, it is apparent that the preventation of thromboembolism is independent of blood oxygen concentration and blood pressure.

EXAMPLE 3

A composite of a polymethyl methacrylate powder and a coherent polymethyl methacrylate base was mounted to the strut of a porous metal coated heart valve cage and placed in the right atrium of a dog. After 6 months, the dog was still alive and well, indicating probable endothelialization of the polymethyl methacrylate porous surface.

EXAMPLE 4

A 20% solution of a hydrophilic polyurethane consisting of urea interlinked blocks of polyether and chain extended urethane in dimethyl formamide and containing 4 g of polymer was slurried with 10 g of sodium chloride crystals of average size −200 +500 mesh. The slurry was dried in a vacuum oven to remove the solvent. The polymer coated salt was placed in a mold and

compression molded at 300° to 350° F (150° to 175° C) for about 15 minutes. The mold was cooled and the sample removed.

After removal from the mold, the sample was immersed in a beaker of hot water and squeezed from time to time to assist in salt removal. After completion of the salt leaching, a porous spongy polymer product with interconnected pores resulted. The product had the microscopic appearance seen in FIGS. 7 and 8.

SUMMARY

The present invention, therefore, provides novel cardiovascular devices or implants which have biocompatibility and hence avoid the prior art thrombogenic problems. Modifications are possible within the scope of the invention.

What I claim is:

1. A heart valve structure comprising an occluder, an occluder seating ring and occluder guide means, each of said occluder seating ring and occluder guide means being constructed of metal inert to blood and consisting of a dense rigid, coherent metal substrate and a rigid porous metal coating adhered to at least a substantial portion of said substrate, said porous metal coating including a plurality of metal particles bonded together at their points of contact with each other and with said substrate to form a network of interconnected pores substantially uniformly distributed through the coating, said porous coating having a porosity of about 10 to about 50% and a thickness of about 20 to about 300 microns, said porous coating and the coating-substrate interface having a shear strength greater than about 1000 psi, the composite of said porous coating and substrate having a high fatigue tolerance, said metal particles having a particle size of −500 mesh.

2. The heart valve structure of claim 1 wherein said porous coating has a thickness of about 50 to about 150 microns, said shear strength is greater than about 3000 psi, and said composite has an endurance limit after 10^7 cycles of greater than about 500 psi.

3. The heart valve structure of claim 1 including metal muscle guard means consisting of a dense rigid coherent metal substrate and said rigid porous metal coating adhered thereto.

4. The heart valve of claim 3 including a layer of polymeric material overlying and adhering to said porous metal coating on at least said occluder guide means, said layer of polymeric material comprising a dense coherent polymeric substrate interlocking with the interconnected pore network of the porous metal coating.

5. The heart valve of claim 4 wherein said polymeric substrate has an adhered porous polymeric coating having a plurality of interconnected pores therein.

6. A heart valve structure comprising an occluder, an occluder seating ring having sewing ring mounting means, occluder guide means, and a flexible sewing ring constructed of polymeric material inert to blood and body fluids and adhered to said sewing ring mounting means, each of said occluder seating ring and occluder guide means being constructed of metal inert to blood,

at least a substantial proportion of each of occluder seating ring and occluder guide means consisting of a dense rigid coherent metal substrate and a rigid porous metal coating adhered to said substrate,

said porous coating including a plurality of metal particles bonded together at their points of contact with each other and with said substrate to form a network of interconnected pores substantially uniformly distributed throughout said coating,

said sewing ring comprising an outer layer of porous polymeric material having a plurality of interconnected pores distributed therethrough adhered to a flexible coherent polymeric substrate,

said sewing ring being adhered to said sewing ring mounting means by interlock of said flexible coherent polymeric substrate in the interconnected pore network of the porous metal coating on said sewing ring mounting means.

* * * * *

US005843172A

United States Patent [19]

Yan

[11] Patent Number: 5,843,172

[45] Date of Patent: Dec. 1, 1998

[54] **POROUS MEDICATED STENT**

[75] Inventor: **John Y. Yan**, Los Gatos, Calif.

[73] Assignee: **Advanced Cardiovascular Systems, Inc.**, Santa Clara, Calif.

[21] Appl. No.: **842,660**

[22] Filed: **Apr. 15, 1997**

[51] **Int. Cl.**[6] **A61F 2/06**

[52] **U.S. Cl.** **623/1**; 623/2; 606/198; 606/191; 604/104

[58] **Field of Search** 623/1, 2, 12; 606/191, 606/195, 198, 153; 604/104, 107

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,855,638	12/1974	Pilliar	623/16
4,101,984	7/1978	MacGregor	623/2
4,355,426	10/1982	MacGregor	623/1
5,163,958	11/1992	Pinchuk .	
5,370,684	12/1994	Vallana et al. .	
5,419,760	5/1995	Narciso, Jr.	623/12
5,441,515	8/1995	Khosravi et al.	623/12
5,571,187	11/1996	Devanathan	623/16
5,624,411	4/1997	Tuch .	
5,630,840	5/1997	Mayer .	
5,632,779	5/1997	Davidson .	
5,697,967	12/1997	Dinh et al.	623/1
5,707,385	1/1998	Williams	604/104
5,725,567	3/1998	Wolff et al.	623/1

FOREIGN PATENT DOCUMENTS

WO 95/11817 5/1995 WIPO .

WO 96/28115 9/1996 WIPO .

OTHER PUBLICATIONS

Lambert, Thomas L., M.D., et al., Localized Arterial Wall Drug Delivery From a Polymer–Coated Removable Metallic Stent, *Circulation,* Eol. 90, No. 2 (Aug. 1994) pp. 1003–1011.

De Scheerder, Ivan K, et al., Biocompatibility of Polymer–Coated Oversized Metallic Stents Implanted in Normal Porcine Coronary Arteries, *Atherosclerosis,* vol. 114 (1995), pp. 105–114.

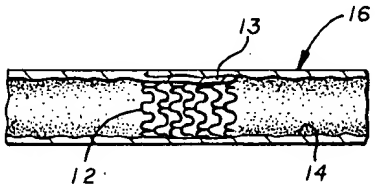
Primary Examiner—Paul B. Prebilic

Attorney, Agent, or Firm—Fulwider Patton Lee & Utecht, LLP

[57] **ABSTRACT**

A medicated prosthesis, such as a stent, is deployed in a human vessel. A metallic stent has a plurality of pores in the metal which are loaded with medication. When the stent is implanted into the vasculature of a patient, the medication in the stent dissipates into the tissue of the vasculature proximate the stent. The stent may be formed from a porous metal in the form of a wire, tube, or metal sheet. The present invention also includes a method of treating vasculature disease by delivering medication to the site of the vascular disease including the step of deploying a metal stent having a plurality of pores in the stent and further having medication in the pores and delivering the stent to the site of vasculature disease.

27 Claims, 5 Drawing Sheets



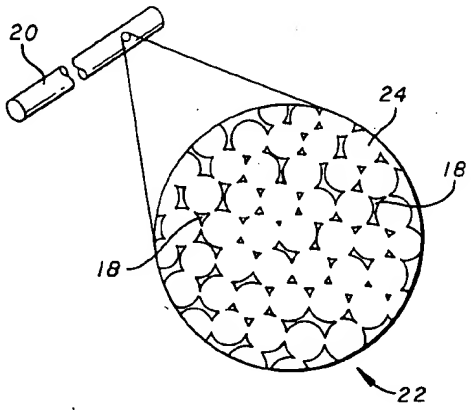
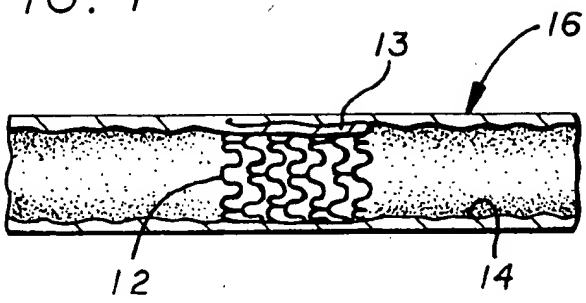


FIG. 1



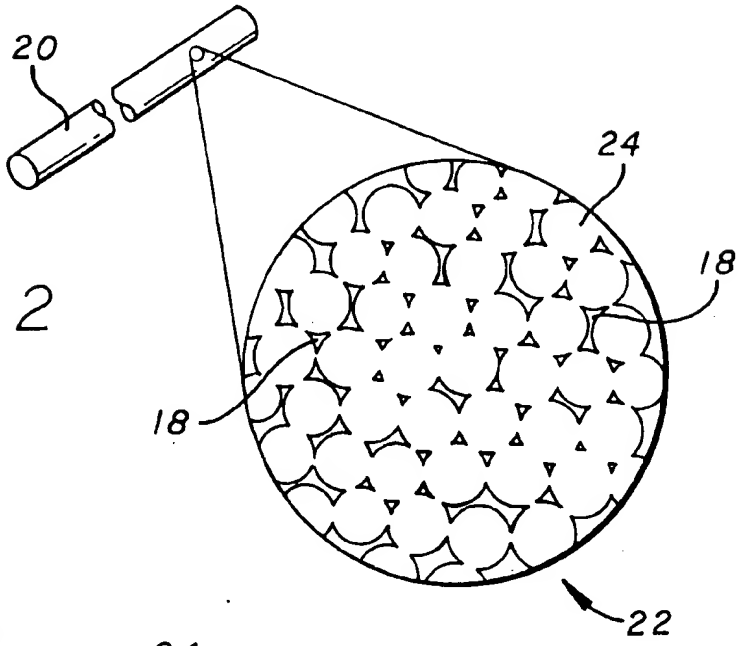


FIG. 2

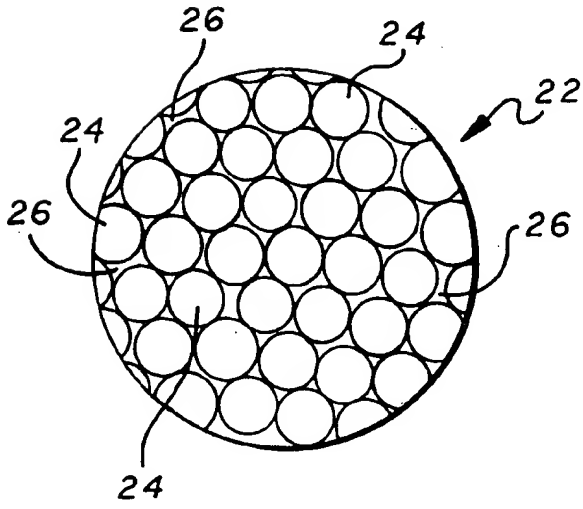
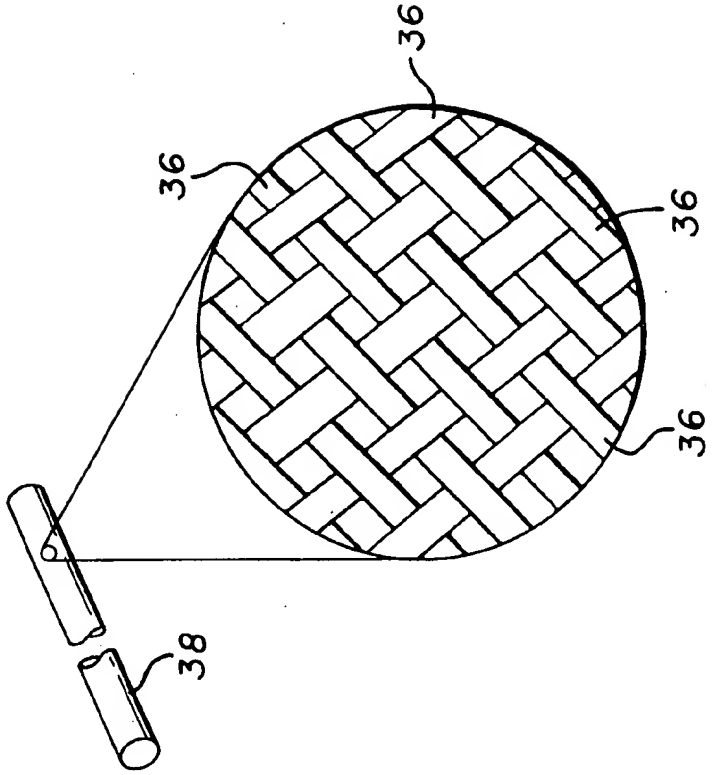


FIG. 3

FIG. 5



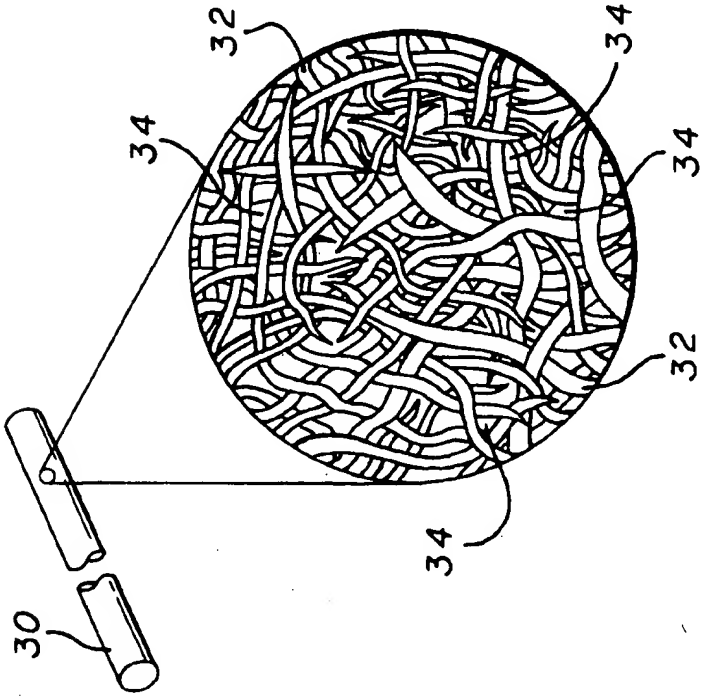
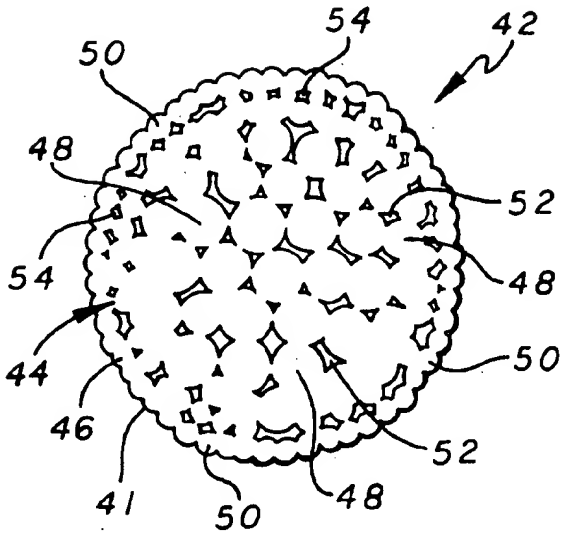


FIG. 4



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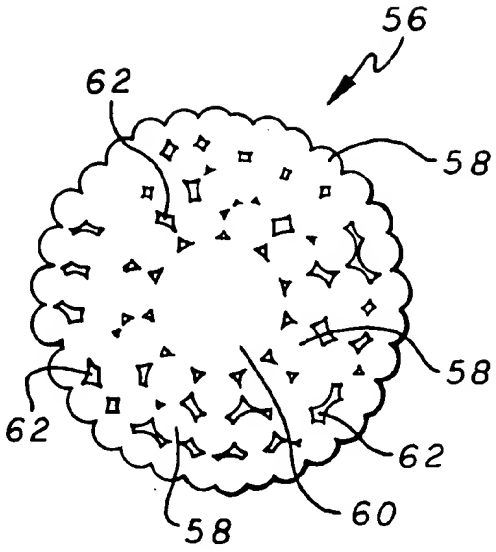


FIG. 7

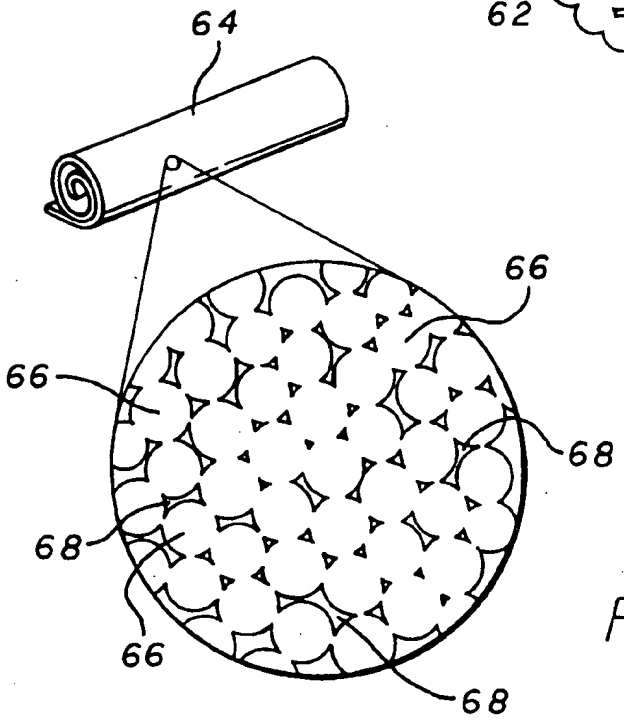
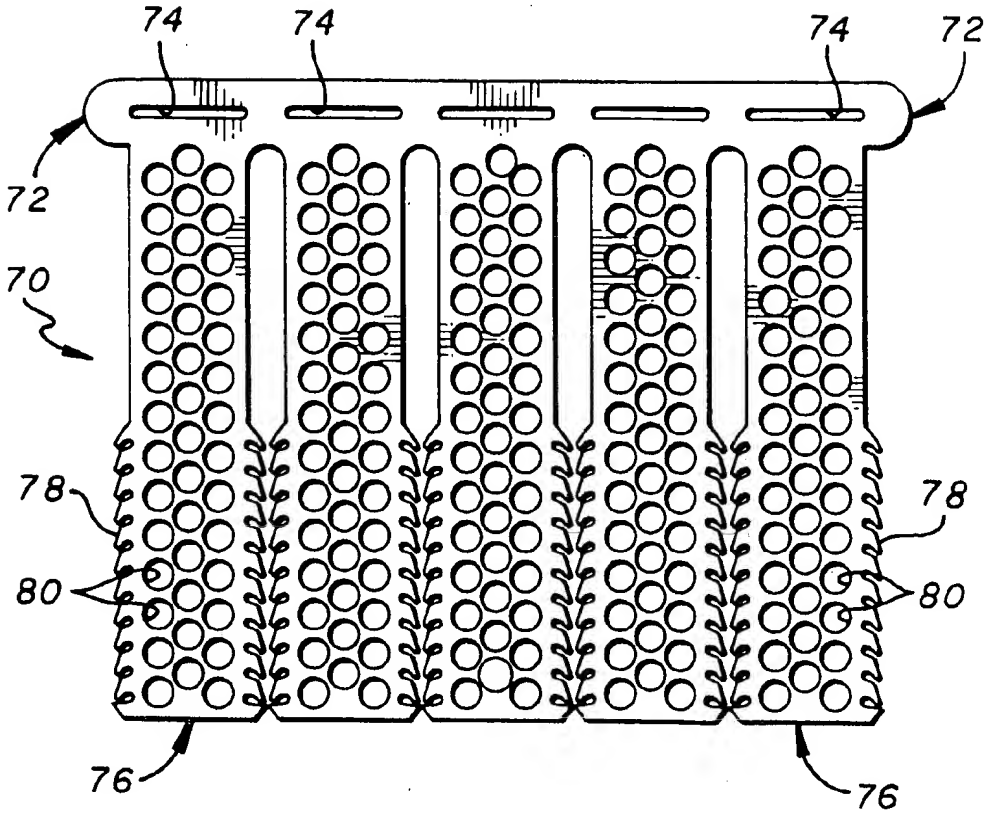


FIG. 8

FIG. 9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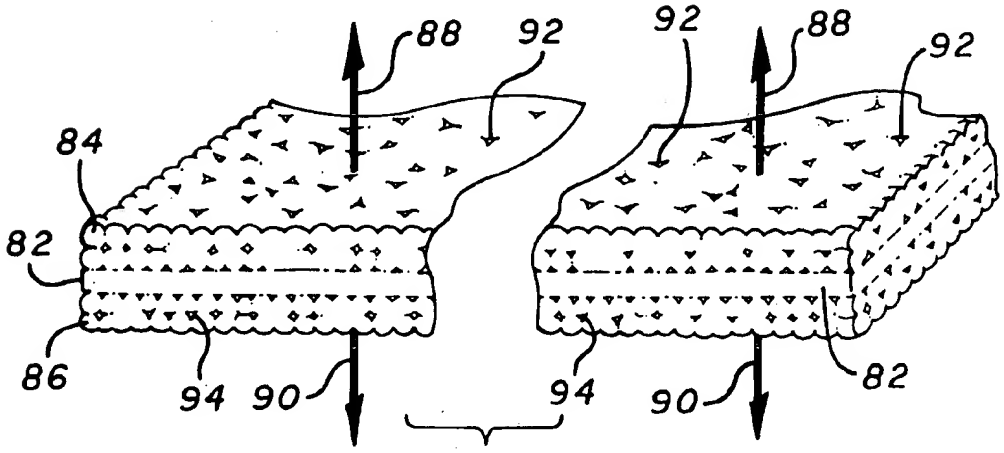
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FIG. 10

FIG. 11

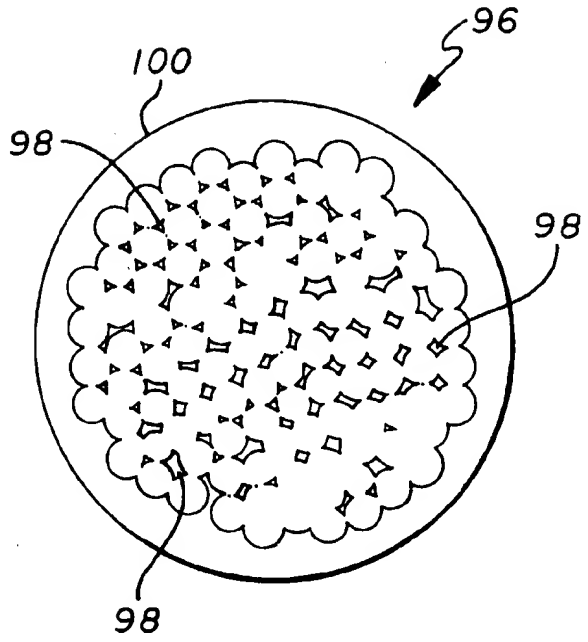
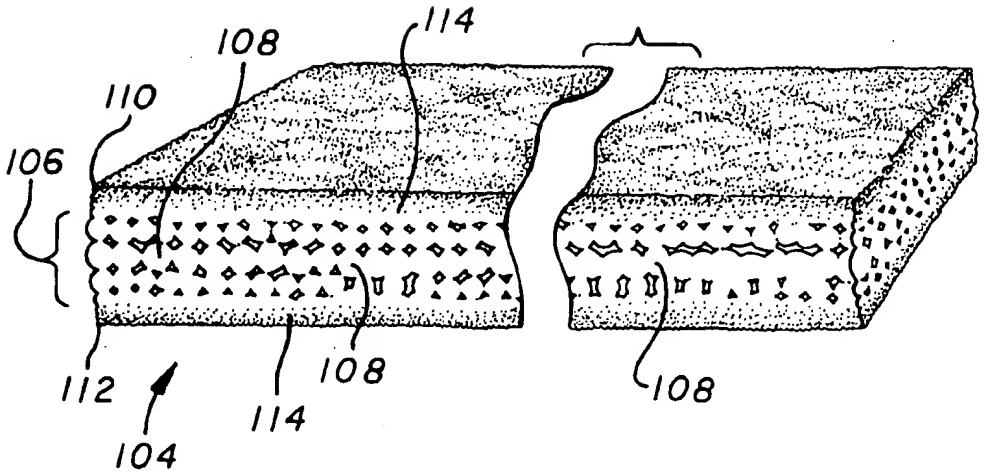


FIG. 12



POROUS MEDICATED STENT

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention generally relates to a medicated prosthesis or implant. More particularly, the invention relates to a medicated intra-vascular prosthesis, such as a stent, that is radially expandable in the vasculature of a patient and delivers a therapeutic agent to the site of the implantation.

2. Description of Related Art

Stents are generally cylindrically shaped prosthetic implants which function to hold open and sometimes expand a segment of a blood vessel or other anatomical lumen. They are particularly suitable for supporting and preventing a torn or injured arterial lining from occluding a fluid passageway. Intravascular stents are increasingly useful for treatment of coronary artery stenoses, and for reducing the likelihood of the development of restenosis or closure after balloon angioplasty.

The success of a stent can be assessed by evaluating a number of factors, such as thrombosis; neointimal hyperplasia, smooth muscle cell migration and proliferation following implantation of the stent; injury to the artery wall; overall loss of luminal patency; stent diameter in vivo; thickness of the stent; and leukocyte adhesion to the luminal lining of stented arteries. However, the chief areas of concern are early subacute thrombosis, and eventual restenosis of the blood vessel due to intimal hyperplasia.

Therapeutic pharmacological agents have been developed to improve successful placement of the stent and are delivered to the site of stent implantation. Stents that are of a common metallic structure were previously unable to deliver localized therapeutic pharmacological agents to a blood vessel at the location being treated with the stent. There are polymeric materials that can be loaded with and release therapeutic agents including drugs or other pharmacological treatments which can be used for drug delivery. However, these polymeric materials may not fulfill the structural and mechanical requirements of a stent, especially when the polymeric materials are loaded with a drug, since drug loading of a polymeric material can significantly reduce the structural and mechanical properties of the polymeric material.

It has been known in the art to coat a metallic stent with a polymeric material and load the polymeric material with a drug. Alternatively stents of polymeric materials have been reinforced with metal structure. These stent designs have the strength necessary to hold open the lumen of the vessel because of the reinforced strength of the metal. Stents made of both polymeric material and metal have a larger radial profile because the volume occupied by the metal portion of the stent cannot absorb and retain drugs. Reducing the profile of a stent is preferable because it increases the in vivo diameter of the lumen created by the stent. Thus it is desirable to configure a metallic stent to deliver drugs to the blood vessel walls without substantially increasing the profile of the stent. The present invention meets these needs.

SUMMARY OF THE INVENTION

Briefly, and in general terms, the present invention provides for an implantable prosthesis that is made of metal and has porous cavities in the metallic portion of the prothesis so that the drugs can be loaded directly into the pores without substantially weakening the structural and mechanical characteristics of the prosthesis. The stent of one embodiment of the present invention can be implanted in the specific site of vascular injury such as can occur from balloon angioplasty or de novo lesions of a therosclerotic disease. The drugs in the pores of the stent can treat restenosis, tissue inflammation, promote endothelialization or any other disease that may inhibit the successful implantation of a stent.

In one embodiment of the invention, the porous cavities of the stent can be formed by sintering the stent material from metallic particles, filaments, fibers or other materials. The stent can be formed from a sintered wire that is coiled or otherwise formed into a stent. The stent can be formed from a sintered cylindrical tube or sintered metal sheet which can be laser cut or chemical etched into an expandable stent structure.

Additionally, the porosity of the stent metal can be increased by using particles that are not spherical such as fibrous particles, filaments or wires. In one embodiment of the invention, the interwoven fibers and filaments can also be sintered after they are woven into the desired shape.

In one embodiment of the present invention, the stent is formed from a metal wire or strut that is formed of a first layer of particles oriented along an axis forming a core and an outer layer of particles arranged radially outward from the inner layer of particles. The outer layer of particles has a smaller diameter than the inner layer of particles. This embodiment has the advantage that the stent can hold more of the drugs in the center of the stent. The smaller diameter particles on the outside controls the rate at which drugs are released into the walls of the vessel. The larger diameter particles create cavities of greater porosity to hold a larger volume of medication.

In another embodiment it may be desirable to form a stent having a solid core and a porous outer section. This can be accomplished by sintering particles to a solid non-porous metal wire. A stent so configured has a solid core which reinforces the structure of the stent. The porous particles sintered to the surface of the stent absorb drugs for delivery.

In one embodiment according to the present invention, the stent is formed from a sheet or tube of sintered metal. The sheet or tube is cut according to a pattern that allows the stent to be expanded and deployed into the vasculature. The stent pattern of this embodiment can be stenciled onto the sheet or tube of sintered metal and then may be cut by laser cutting the sheet into the desired shape. Alternatively, the stent can be chemical etched into its desired shape.

According to another embodiment of the invention, the stent receives a coating on the surface of the stent. In certain applications, it is desirable that the coating be a bio-polymer and in other applications, the coating preferably is a synthetic polymer or a hydrogel. The coating can also be a heparin coating that is affixed to the surface of the stent through ionic bonding, end point attaching or photolinking the heparin.

The coating is preferably permeable to the medication according to one embodiment of the invention. The permeability of the coating should be selected to release the medication in the stent at a desired rate. In another embodiment of the present invention, a bioabsorbable coating is applied to the stent. This coating is dissolved by the body fluids. Furthermore, it is desirable in certain applications to load medication into the coating applied to the stent. The coating, according to one application is preferably the same drug or medication that is loaded into the stent in one embodiment. In other embodiment, the coating is loaded with a different medication. In this configuration, two medications are released in a sequential manner.

The present invention also includes a method of using a medicated prosthesis. The method comprises of providing a porous prosthesis, loading a drug into the porous cavity of the prosthesis, positioning the prosthesis in an appropriate site and affixing the prosthesis to the site. In another embodiment, the metal further includes the step of applying a coating to the stent after the step of loading the drug into the porous cavities of the stent.

These and other features of the present invention will become apparent from the following more detailed description, when taken in conjunction with the accompanying drawings which illustrate, by way of example, the principles of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a longitudinal sectional view of a blood vessel with stent manufactured according to one embodiment of the present invention.

FIG. 2 is a porous stent wire or strut in a partially magnified, partially cut away perspective manufactured according to one embodiment of the present invention.

FIG. 3 is a magnified, cross-sectional view of unsintered packed particle.

FIG. 4 is a porous stent wire or strut in partially magnified, partially cut away perspective manufactured according to one embodiment of the present invention.

FIG. 5 is a porous stent wire or strut in partially magnified, partially cut away perspective manufactured according to one embodiment of the present invention.

FIG. 6 is a cross-sectional view of a stent wire or strut manufactured according to one embodiment of the present invention.

FIG. 7 is a cross-sectional view of a stent wire or strut manufactured according to one embodiment of the present invention.

FIG. 8 is a sheet of sintered stent manufactured according to one embodiment of the present invention.

FIG. 9 is a stent formed from a sheet of sintered metal according to one embodiment of the present invention.

FIG. 10 is a cross-sectional, partially cut away view of a sheet of sintered metal manufactured according to the principles of one embodiment of the present invention.

FIG. 11 is a cross-sectional view of a stent wire or strut manufactured according to the principles of one embodiment of the present invention.

FIG. 12 is a cross-sectional view, partially cut away of a sheet of sintered metal manufactured according to the principles of one embodiment of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Referring now to FIG. 1, the prosthesis of one embodiment is a porous stent 12 that is radially expandable against the walls 14 of a vessel 16. The stent is loaded with a therapeutic agent in the pores (18 of FIG. 2) of the stent. When placed in the vasculature, the therapeutic agent is delivered to the tissue that comes into contact with the stent. The stent of one preferred embodiment is formed of a stent wire that is porous. An example of a porous stent wire is a sintered metal wire. FIG. 2 illustrates a partial microscopic view of a sintered wire that is suitable for use in one embodiment of the present invention. The wire is porous and has several porous cavities 18. The size of the cavities preferably range between 0.01 and 20 microns in size.

Porous metal is made, according to one preferred embodiment, by the process of sintering metal. Sintering is a process of fabrication where particles are bonded together without entirely melting the particles. Particles are pressed together or molded into a desired shape. A considerable amount of pressure is first applied to press the particles together. Then, the metal is heated to temperatures slightly below the melting point of the metal. Without entirely melting, the particles bond to each other at their respective surfaces. Space remains between the lattice of the particles which define the porous cavities 18.

The formation of sintered metal is illustrated with reference to FIG. 3 and continued reference to FIG. 2. FIG. 3 is a microscopic view of a packed lattice 22 of metallic particles 24. Gaps 26 exist between each particle despite the fact that the particles are pressurized and are in contact with adjacent particles. Particles are preferably sized between 0.02 microns and 20 microns in diameter. Prior to heating, there are no chemical bonds formed between the individual particles. When the metal is heated to slightly below the melting point of the metal, the particles bond with neighboring particles. The gaps in the packed lattice form pores 18 when the particles are sintered. Thus in FIG. 2, the metal stent wire formed by the process of sintering has porous cavities 18 extending throughout the entire wire, thereby interconnecting the cavities. The cavities then can be filled with a therapeutic agent as hereinafter described. The appropriate pressure and temperature of sintering a particular metal is specific to that particular metal. One skilled in the art of metal fabrication would understand how to sinter any given metal or alloy.

For each of the embodiments, the metal stent material member can be a suitable metal such as stainless steel, tantalum, nickel-titanium alloy, platinum-iridium alloy, molybdenum-rhenium alloy, gold, magnesium, combinations thereof, although other similar materials also may be suitable. The metal can be modified to exhibit different hardnesses, and thus varying stiffnesses, by well known annealing and manufacturing processes.

One of the most important factors to be considered when making a stent according to one embodiment of the present invention is the porosity of the metal. Porosity is the total volume of pores in the sintered metal divided by the total volume of the metal. Porosity determines the amount of a therapeutic agent that can be loaded into a stent of predetermined dimensions. High porosity means that a stent can deliver more therapeutic agents or have a narrower profile because it is less dense. High porosity, according to some embodiments of the present invention, adversely affects the strength and elasticity of a metal. Consequently, there is an ongoing tradeoff between stent strength, on the one hand, and stent profile and stent load capacity on the other hand.

Pore size is a function of particle size and dimension. In one embodiment of the present invention illustrated in FIG. 3, the particles 24 are generally spherical. Size of the pore 18, particularly with generally spherical particles, is proportional to particle size. When the particles 24 have inconsistent size, smaller particles tend to fill the gaps between the larger particles. Thus, the porosity of such particles are less predictable. Consistent pore size is also important to ensure that drugs are evenly distributed throughout the stent. Consistent distribution on the other hand ensures that the tissue in contact with the stent will receive an even distribution of a therapeutic agent.

There are several types of drugs that are currently administered at the site that a stent is placed in the vessel.

Examples of therapeutic drugs, or agents that can be combined with the polymeric layers include antiplatelets, anticoagulants, antifibrins, antithrombins, and antiproliferatives. Examples of antiplatelets, anticoagulants, antifibrins, and antithrombins include but are not limited to sodium heparin, low molecular weight heparin, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antibody, recombinant hirudin, thrombin inhibitor (available from Biogen), and 7E-3B® (an antiplatelet drug from Centocore). Examples of cytostatic or antiproliferative agents include angiopeptin (a somatostatin analogue from Ibsen), angiotensin converting enzyme inhibitors such as Captopril® (available from Squibb), Cilazapril® (available from Hoffman-LaRoche), or Lisinopril® (available from Merck); calcium channel blockers (such as Nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, Lovastatin® (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug from Merck), methotrexate, monoclonal antibodies (such as to PDGF receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitor (available from Glazo), Seramin (a PDGF antagonist), serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. Other therapeutic drugs or agents which may be appropriate include alpha-interferon and genetically engineered epithelial cells, for example.

While the foregoing therapeutic agents have been used to prevent or treat restenosis, they are provided by way of example and are not meant to be limiting, since other therapeutic drugs may be developed which are equally applicable for use with the present invention. The treatment of diseases using the above therapeutic agent are known in the art. Furthermore, the calculation of dosages, dosage rates and appropriate duration of treatment are previously known in the art.

The therapeutic agent of one embodiment is preferably in liquid form and is loaded into a stent by immersing the stent in a medicated solution. The therapeutic agent may be dissolved in a solvent or suspended in a liquid mixture. If a suspension of drugs are used, it is important that the pore size of the stent is considerably larger than the therapeutic agent. An average pore size that is more than ten (10) times the particle size of a suspended therapeutic agent is suitable. After the stent is emersed in the medicated solution, the therapeutic agent absorbs into the pores of the stent. At which time, the loaded stent can be removed from the solution and implanted into the vasculature of a patient. Additionally, a therapeutic agent can be loaded into the stent by applying pressure to the fluid to aid the passage of medicated fluid into the porous cavities of the stent. This can be done similar to how fluid can be pressurized through the pores of a filter.

Once loaded, the therapeutic agent remains in place by the surface tension between the walls **28** of the several porous cavities **18** and the therapeutic agent. As shown in FIG. **1**, the loaded or medicated stent **12** is then deployed to the site of arterial closure **13** and is expanded. The expanded stent engages the walls **14** of the vessel **16** to maintain the patency of the vessel. Once in the vessel, the therapeutic agent disseminates from the porous cavities **18**, as depicted in FIG. **2**, of the stent and is absorbed into the tissue of the walls of the vessel that are in contact with the stent.

The advantage of the stent of the present invention over prior art medicated stents is one of profile and strength. Metal, including sintered metal, is stronger than synthetic materials that are capable of being loaded with a therapeutic agent. Thus, in order for a medicated stent to deliver an appropriate amount of a therapeutic agent and structurally maintain vessel patency, the profile of the stent must be substantially larger than metal stents. This is true whether a metal stent is coated with a therapeutic agent, or if the stent is entirely made of a plastic material.

Sintered metal has strength and elasticity that is comparable to regular metal. Sintered metal furthermore has the added feature that it is porous. Consequently, a sintered stent can be made having a profile that is substantially comparable to a conventional metal stent. Yet, a therapeutic agent can be loaded into the pores and delivered to the site of stent implantation without the aid of medicated coatings.

Additionally, many synthetic materials, including materials that are bioabsorbable, cause inflammation of the tissue. A medicated stent that has a therapeutic agent loaded directly into the pores of the stent can avoid synthetic coatings that have been known to cause irritation at the site of stent implantation.

FIG. **4** illustrates an alternative embodiment of a stent wire **30** constructed according to the present invention. The stent is formed of elongated particles **32**, i.e., filaments and fibers. Sintered particles (**24** of FIG. **2**) that are generally spherical in shape are capable of forming sintered metal having a porosity in the range of 0.30 to 0.05. However, when filaments or fibers **32** are sintered, the porosity can be increased above 0.30. The technique of fabricating a stent with elongated filaments or fibers are similar to the method described above for spherical particles or powders. The filaments or fibers are molded and pressurized. Then the fibers are heated to a temperature just below the melting point of the metal.

Greater porosity of a stent made of metal filaments or fibers **32** rather than spherical particles (**24** of FIG. **2**) is obtained because of the irregular shape of the particles. The particles cannot be packed as tightly as regular generally spherical particles. Furthermore, the particles can be packed less densely and still maintain contact between the particles to allow sintering. Thus, the void space or pores **34** in the sintered metal are larger.

The strength of a stent wire **30** using filaments in FIG. **4** is improved because the individual strands have larger surface area to volume and contact a greater number of neighboring strands. Thus, each filament or fiber will have a larger bonding surface and may bond with a greater number of neighboring fibers. A matrix of overlapping filaments or fibers is thus formed with greater porosity and stronger inter-particle bonding.

In yet another embodiment, wire fibers **36** are woven or twined into a structure **38** as illustrated in FIG. **5**. The individual strands cooperate in a synergistic manner to reinforce the strength of the wire. Additionally, the wire fibers can be woven into the form of a sintered metal sheet having improved and reinforced strength or a sintered metal tube. Other combinations of particle size and shape can be employed to form a stent wire having different characteristics.

In another embodiment illustrated in FIG. **6**, the stent wire **42** is formed of an inner core **44** and an outer layer **41** of sintered particles. The outer layer is formed from articles having a different diameter than the diameter of the particles that form the inner core. For example, the core of the metal is formed of particles that have a diameter in the range of 10–20 microns at the core of the wire. Surrounding the core

are particles that have a diameter in the range of 2–4 microns on the outer surface. The larger particles create a core having larger pores **52**. This results in higher porosity and thus a higher load capacity. The smaller particles on the outer layer form smaller pores **54** which reduce the rate of diffusion of drugs into the tissue of the vessel.

When a therapeutic agent is loaded into a stent formed of the stent wire **42** illustrated in FIG. **6** a larger volume can be stored in the larger pores **52** at the core **44** of the stent wire. Once the stent is placed into the vessel, the therapeutic agent in the stent wire is delivered at a rate determined by the smaller pores **54** in the outer layer **46** of the stent wire. Such a structure is expected to have a benefit of being able to store a large amount of therapeutic agent at the core and deliver the therapeutic agent at a slower rate. Consequently, this design is desirable for low-dose, long-term drug therapy.

Alternatively, according to another embodiment of the present invention shown in FIG. **7**, a stent wire **56** is formed from sintered particles **58**. The pores **62** formed between the sintered metal particle surrounding the solid core retain the therapeutic agent. The total porosity of a stent having a solid core and porous outer layer is much lower than a stent wire of similar proportion that is entirely made of sintered particles. However, the solid core reinforces the tensile strength and elasticity of the metal stent and is considerably stronger. Thus, it is desirable to use a sintered stent with a solid core for applications where maximum tensile strength and elasticity is desirable and only a relatively small amount of therapeutic agent is needed.

The sintered metal stent of yet another embodiment of the present invention can be made of material formed in different shapes than sintered metal. For example, the stent can be formed of a sheet of sintered metal as shown in FIG. **8** or a sintered metal tube. By way of example, metal particles **66** are arranged and pressurized into a sheet. The sheet is heated to a temperature below the melting point of the particles as described previously. The sheet of sintered metal is porous and has a plurality of pores **68**.

The same principles that apply to porosity and pore size of a wire apply equally to a sintered stent that is formed into a sheet or tube. The advantage of forming the stent from a sheet of metal is that the stent is radially expandable without placing a great deal of strain on the metal lattice when it is expanded. A sheet or tube of sintered metal can be cut in the desired shape to form the metal structural member with a laser, such as a continuous CO_2 laser, a pulsed YAG laser, or an excimer laser, for example, or alternatively, by chemical etching or stamping. When cut from a flat sheet, the stent is then rolled into a cylindrical configuration and laser welded along the longitudinal edges.

The stent can be formed into a particular pattern known in the art for stents formed from metal sheets. One such pattern is a rolled locking design and is illustrated in FIG. **9**. The sheet is etched into a stent configuration that has a head portion **72** that includes one or more slots **74** for receipt of a like number of tail portions **76**. The tail portions are received into the slots so as to form a cylindrical loop. The tail end includes a plurality of teeth **78** adapted to cooperatively engage the slot of the head portion. When the teeth engage the slot, the tail is retained in place in an expanded state. Additionally, holes **80** are formed throughout the stent to reduce the metal-to-air ratio of the stent. The less metal in contact with the wall **14** of the vessel **16**, the better the blood compatibility of the stent.

Prior to deployment, the tail end is coiled into a retracted position. The tail is threaded through the slot and wound. It is expanded by a balloon according to principles that are well known in the art for delivering and implanting a stent. As the stent is expanded by a balloon during deployment it unwinds and the teeth lock into the slots at a desired radial diameter to prevent the stent from returning to its original retracted state.

A benefit of the coiled stent shown in FIG. **9** is that the stent **70** can be etched to have a minimal surface area that comes in contact with the walls of the vessel. This may be an important feature when it is desired to cover an entire portion of the walls of a blood vessel with a therapeutic agent because the coiled sheet metal stent can be configured to maintain maximum surface area contact with the wall of the blood vessel in contrast to wire stents.

With reference to FIG. **10**, another embodiment of the present invention is a sheet formed of sintered particles that are sintered to both sides **84** and **86** of a metal sheet **82**. The stent of FIG. **10** is similar in structure to the stent wire of FIG. **7** that has a solid core and has porous particles sintered to the core forming a porous outer layer. The solid core reinforces the strength of the metal. The metal sheet also provides a barrier through which a therapeutic agent cannot pass. Thus, a therapeutic agent loaded into the pores **92** on the top side of **84** the sheet permeates in a first direction **88** outward from the solid core. A therapeutic agent loaded into the pores **94** on the bottom side **86** of the solid wire permeates only in a second direction **90** opposite to the direction of the therapeutic agent loaded into the pores on the top side.

When a stent as shown in FIG. **10** is looped into a cylindrical formation and placed into a vessel, only the top side **84**, which is directed radially outward, engages the walls of the vessel. The bottom side **94** faces radially inward and does not come in contact with the walls of the vessel. Thus, if it is desired, a first therapeutic agent can be loaded into the top side to treat the tissue in the wall of the vessel. A second therapeutic agent can be loaded into the bottom side to prevent coagulation of the blood flowing in the vessel. Additionally, the stent can be formed so that particles are sintered only to one side of the stent. A therapeutic agent is loaded into the sintered metal on the porous side of the stent. When a stent is formed from a one-sided porous stent, it can be oriented radially outward to deliver a therapeutic agent to the tissue in the wall of the stent.

FIG. **11** illustrates a cross-sectional view of a stent wire of strut according to one embodiment of the invention. The sheet has a plurality of porous cavities or pores **98**. A therapeutic agent is loaded into the pores of the sintered metal. Then, a coating **100** is applied to the sintered metal. The coating may be used for several purposes as illustrated hereinafter.

With reference to FIG. **12**, another embodiment of the invention is shown wherein the stent is formed of a sintered sheet **104** of metal having core **106** formed of large diameter particles **108** that form large pores. The core layer **106** is sandwiched between two layers **110** and **112** formed of smaller diameter particles **114** or particles that form smaller diameter pores. Such a sheet is formed by orienting a middle or core layer **106** of large diameter particles along a plane. A top layer of smaller diameter particles is arranged in a plane parallel to and above the middle layer. A bottom layer of particles are arranged in a plane parallel to and below the middle layer. The three layers are pressed together and sintered into a single sheet. The sheet can then be cut or etched into a stent configuration.

While one of the benefits of the present invention is to provide a stent that does not require a coating for the purpose

of delivering a therapeutic agent to the blood vessel, the application of a coating after a therapeutic agent is loaded into the pores of the sintered metal does not defeat the utility of the present invention. For example, when a therapeutic agent is loaded into the pores of the stent and into a polymeric coating, the profile of the polymeric coating can be reduced. Alternatively, a larger dosage of a therapeutic agent can be delivered to the site of stent implantation. Additional benefits are observed by loading a stent with a therapeutic agent in the pores of the metal and then further applying a coating to the stent. Furthermore, even if a coating is applied to the stent, the principles of reducing profile and reinforcing the stent are still apparent because a greater volume of therapeutic agent can be delivered by a coated sintered stent than a coated, solid stent have comparable dimensions.

The polymeric material that coats a sintered metal stent of the invention preferably comprises a biodegradable, bioabsorbable polymeric film that is capable of being loaded with and capable of releasing therapeutic drugs. The polymeric coatings preferably include, but are not limited to, polycaprolactone (PCL), poly-DL-lactic acid (DL-PLA) and poly-L-lactic acid (L-PLA) or lactide. Other biodegradable, bioabsorbable polymers such as polyorthoesters, polyiminocarbonates, aliphatic polycarbonates, and polyphosphazenes may also be suitable, and other non-degradable polymers capable of carrying and delivering therapeutic drugs may also be suitable. Examples of non-degradable synthetic polymers are Parylene®, Parylast® (from Advanced Surface Technology of Billerica, Mass.), polyurethane, polyethylene, polyethylene teraphthalate, ethylene vinyl acetate, silicone and polyethylene oxide (PEO). The polymeric layers, according to one embodiment is to be loaded with a pharmacologic agent for use in localized drug therapy. As used in this description, the terms biodegradable, bioabsorbable, reabsorbable, degradable, and absorbable are meant to encompass materials that are broken down and gradually absorbed or eliminated by the body, whether these processes are due to hydrolysis, metabolic processes, bulk or surface erosion. In each of the foregoing embodiments, one polymeric layer is preferably 0.002 inches thick.

The thin polymeric films used to coat the stent are preferably first intermixed with the drug or drugs to be delivered, and then are typically laminated or solvent cast to the surface of the metal structural member. Lamination processing methods and temperatures can vary widely depending on the polymers used and the temperature sensitivity of the loaded drugs. Alternatively, the metal structure of the stent can be encapsulated in the layers of polymeric material by solvent casting, melt processing, insert molding, and dip coating.

In one embodiment of the present invention, the membrane is bioabsorbable, but no therapeutic agent is loaded into the polymer. The coating **100** dissolves after implantation and this delays the time that a therapeutic agent is released into the vasculature of a patient. The thickness of the coating as well as the rate at which the coating is bioabsorbed determines the length of time that the stent is mounted into the vascular before a therapeutic agent is delivered from the pores of the stent. Additionally, a therapeutic agent can be loaded into the bioabsorbable coating. Thus a therapeutic agent will be delivered to the stent at a rate determined by the bioabsorbability of the coating. Once the bioabsorbable material has completely dissolved, the therapeutic agent in the pores can be delivered at a rate determined by the pore size and porosity.

In another embodiment, it is preferred that the coating **100** is permeable and non-absorbable. In such circumstances, the rate at which the drugs permeate into the tissue is controlled by the physical properties of the particular coating selected. Additionally, the coating may be selected to reduce restenosis, thrombosis or other tissue inflammation. For example, a heparin coating is known in the art to reduce blood clotting. Heparin, when coated on a stent reduces clotting of blood on the surface of the stent. The heparin coating is affixed to the surface of the stent through ionic bonding, end point attaching, or photo-linking the heparin.

In yet another embodiment, a first therapeutic agent is loaded into the coating and a second therapeutic agent is loaded into the pores of the stent. This may be the case when a series of drug dosages or concentrations are needed. When such a stent is placed into the vasculature, the first therapeutic agent is absorbed first by the stent and a second therapeutic agent is absorbed later by the vasculature. This variation adds a further dimension to drug treatment allowing for sequential drug therapy at the site of placement of a stent.

It will be apparent from the foregoing that while particular forms of the invention have been illustrated and described, various modifications can be made without departing from the spirit and scope of the invention. Accordingly, it is not intended that the invention be limited, except as by the appended claims.

What is claimed is:

1. A medicated stent comprising:

a metallic stent configured to maintain patency of a human vessel, the metallic stent having a plurality of porous cavities;

a therapeutic medication loaded into the porous cavities of the metallic stent; and

a polymeric coating over the surface of the metallic stent wherein the medication in the pores of the stent is a first medication, wherein the coating contains a second medication.

2. The stent of claim **1**, wherein the coating is approximately in the range of 0.0001 inches to 0.002 inches thick.

3. The stent of claim **1**, wherein the coating is a bio-polymer.

4. The stent of claim **3**, wherein the bio-polymer is polylactic acid or fibrin.

5. The stent of claim **1**, wherein the coating is a synthetic polymer.

6. The stent of claim **5**, wherein the coating of the group comprising polyurethane, polyethylene teraphthalate, polyethylene, ethlene vinyl acetate, silicone or polyethylene oxide.

7. The stent of claim **1**, wherein the coating is a hydrogel.

8. The stent of claim **1**, wherein the coating is a heparin coating.

9. The stent of claim **1**, wherein the coating is an ionic heparin coating that is ionic bonded.

10. The stent of claim **1**, wherein the coating is an end point attached heparin coating.

11. The stent of claim **1**, wherein the coating is a photo-linked heparin coating.

12. The stent of claim **1**, wherein the coating is porous and the pores are sized to permit controlled release of the medication through the pores.

13. The stent of claim **1**, wherein the coating is capable of being dissolved by the body fluids.

14. The stent of claim **1**, wherein the coating is configured to reduce the porosity of the stent.

15. The stent of claim **1**, wherein the coating is configured to improve the blood compatibility of the stent.

16. The stent of claim 1, wherein the first medication is an antithrombogenic material.

17. The stent of claim 16, wherein the first medication is of the group comprising heparin, ticlopodine, coumadin, dipyridamole, aspirin, forskolin.

18. The stent of claim 16, wherein the first medication is an $GPII_bIII_a$ blocker.

19. The stent of claim 16, wherein the first medication is an anti-coagulant.

20. The stent of claim 16, wherein the first medication is an anti-fibrin agent.

21. The stent of claim 16, wherein the first medication is an anti-thrombin agent.

22. The stent of claim 16, wherein the first medication is an anti-platelet agent.

23. The stent of claim 16, wherein the first medication is an anti-proliferative agent.

24. The stent of claim 16, wherein the first medication is a radioactive material.

25. The stent of claim 16, wherein the first medication is a vaso-active drug.

26. The stent of claim 16, wherein the first medication promotes endothelialization.

27. The stent of claim 16, wherein the first medication is an anti-inflammatory agent.

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